REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks are respectfully requested.

By the foregoing amendment, Claims 1, 2, 4, 5, 7, 14, 17, 20-21 and 23 have been amended to place the subject application in a better condition for allowance. Support for the amendments can be found throughout the specification. Claim 22 has been canceled without prejudice to or disclaimer of the subject matter recited therein. A clean and a Marked-up copy of a Substitute Specification is attached. Accordingly, all remarks and arguments in this reply will reference the new specification. No new matter has been added.

Substitute Specification:

Turning now to the Official Action, the Examiner has objected to the substitute specification filed 9 March, 2002 for allegedly not containing a clean copy. Applicants hereby submit another substitute specification in proper idiomatic English and in compliance with 37 C.F.R. § 1.52(a) and (b) along with this response. A marked-up copy of the specification, showing the amendments made via the substitute specification, and a clean copy are attached. For clarity and completion, Applicants have also included amendments to the specification from the Amendment and Reply filed on February 6, 2001, already made of record by the Examiner. In particular, a paper copy of the sequence listing (filed on February 6, 2001) has been added after the last page of the substitute specification, currently page 27. Additionally, please find attached as Exhibit A the

drawing entitled "Pathway for the Biosynthesis of Caffeine." Please amend the remaining page numbers accordingly. This substitute specification is in full compliance with the sequence listing rules set forth in 37 C.F.R. §§ 1.821-.825. Applicants submit that no new matter has been added with regard to the substitute specification. Entry of this substitute specification is respectfully requested.

Claims Rejected Under 35 U.S.C. § 112, First Paragraph:

The Examiner has rejected Claims 1-2, 4-5, 7, 13-14, 16-17, 20-23 and 27-28 under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for nucleic acids of SEQ ID NO:2 or those encoding SEQ ID NO:1 and plant cells and plants transformed with those nucleic acids, allegedly does not reasonably provide enablement for nucleic acids that encode SEQ ID NO:1, encode modified nucleic acids or that hybridize under unspecified stringency to nucleic acids that encode SEQ ID NO:1.

Specifically, the Examiner alleges that undue experimentation is needed because the specification fails to provide guidance regarding which amino acids can be deleted or which regions of the protein can tolerate insertions to continue producing a functional enzyme. Applicants respectfully traverse this rejection.

MPEP § 2164 recites that the disclosure must "contain sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. . ." without undue experimentation.

It is well within the purview of the skilled artisan and the teachings of the subject specification to modify nucleotide sequences by deletion, substitution or insertion and then

determine if such modified sequences maintain the desired enzymatic activity. Further, it is well within the purview of the skilled artisan to produce modified nucleotide sequences and determine if such modified sequences hybridize to the sequence of SEQ ID NO:1 under stringent conditions. Furthermore, it is well within the purview of the skilled artisan to determine if proteins encoded by these modified nucleic acids maintain the recited enzymatic activities. Applicants further submit that the specification, at pages 26-29 (Examples 9-10), teaches how to measure activity of encoded protein. These types of experimentation are merely routine and do not constitute undue experimentation. The specification need not teach what is known in the art (e.g., modifying nucleic acid sequences). In fact, the Federal Circuit has stated that a patent need not teach, and preferably omits, what is well known in the art. *See Hybritech, Inc. v. Monoclonal Antibodies, Ind.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986).

However, in order to expedite prosecution in the subject application, and not to acquiesce to the Examiner's rejection, Applicants have amended Claims 1 and 4, part (b), to recite "a modified nucleotide sequence which hybridizes under stringent conditions to the complementary sequence of said nucleotide sequence (a). . . ." The specification, at pages 5-8, clearly discloses the method for making a modified SEQ ID NO:1, using hybridization under stringent conditions, encoding a polypeptide which maintains all of the N-methyl transferase enzyme activities. Therefore, modification of such amino acid does not involve undue experimentation.

The Examiner further supports his allegations by citing *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 U.S.P.Q. 2d 1016 (Fed Cir. 1991) (Amgen), in the Advisory

Action mailed September 16, 2002. Applicants assert that the case of Amgen is different form the presently claimed invention. In Amgen, Claim 7 which was under review by the court recites:

> "7. A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells and to increase hemoglobin synthesis or iron uptake."

U.S. Patent No. 4,703,008 to Lin, Claim 7.

Amgen claims all "DNA sequence[s] . . . encoding . . . an amino acid sequence sufficiently duplicative of that of erythropoietin . . . ." The Court held that Claim 7 fails to provide a method by which production of DNA analogs is achieved. The Court reasoned that "more is needed concerning identifying the various analogs that are within the scope of the claim, method of making them, and structural requirements for producing compounds with EPO-like activity." *See Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 U.S.P.Q. 2d 1016 , 1028 (Fed Cir. 1991). Unlike Claim 7 in Amgen, the newly amended Claims 1(b) and 4(b) of the present application sufficiently identify the scope within which the claimed analogs fall and further recite methods of producing those analogs. These newly amended Claims 1(b) and 4(b) satisfy the requirements set out by the Court in Amgen by reciting "modified nucleotide sequence which *hybridizes under stringent conditions to the complementary sequence* of said nucleotide sequence . . ." wherein the polypeptide encoded by this modified sequence "*has all of said N-methyl transferase enzyme activities.*" [Emphasis added]. Additionally, the structural requirements for producing such compounds have been disclosed through out the specification and at least at pages 7-11 and 22-29 (Examples 2-10).

Additionally, the Examiner alleges that SEQ ID NO:1 does not appear to be the entire protein sequence. The Examiner alleges that "there is no evidence to suggest that a nucleic acid encoding only SEQ ID NO:1 would function to encode an enzyme with the listed properties, especially since the starting ATG is missing." Applicants respectfully traverse.

Applicants direct the Examiner's attention to the specification, Example 9 - expression of N-methyl transferase in *E. Coli*; (page no. 26). The results shown by this example clearly provide that although SEQ ID NO:1 has not the entire sequence, SEQ ID NO:1 functions to encode an enzyme with the listed properties, even with the starting ATG sequence missing. The specification at page 27, lines 20-23, states that by using the procedures disclosed in Example 9 the encoded isolated enzyme (SEQ ID NO:1), had the listed properties of three different N-methyl transferase activities. Thus in light of the foregoing withdrawal of this rejection is respectfully requested.

The Examiner has rejected Claims 20-23 under 35 U.S.C. § 112, first paragraph, as purportedly lacking enablement. The Examiner alleges that anti-sense suppression of genes is very unpredictable, therefore, it is not certain that such gene will inhibit sense gene transcription or secondary metabolite levels when transformed into a plant of a different species. Furthermore, the Examiner alleges that the specification does not teach production of "ANY" plant metabolite, nor does it provide guidance for altering the "composition" of any plant metabolite.

However, to expedite prosecution in the subject application and not to acquiesce to the Examiner's rejection, Applicants have amended Claims 20, 21 and 23 to further clarify

the claimed invention. As suggested by the Examiner, Claims 20, 21 and 23 have been amended to cancel the phrase "a Camellia" and to limit these claims to only Coffea plants. Furthermore, Claim 20 has been amended to incorporate the limitation of Claim 22. Therefore, it limits the phrase "a secondary plant metabolite" to consist of 7-methyl xanthine, paraxanthine, theobromine, and caffeine. Claim 21 has been amended to limit the phrase "a secondary plant metabolite" to only caffeine. Also, the phrase "modifying a composition" has been replaced by "modifying a concentration" as recommended by the examiner. The phrase "modifying the concentration of caffeine" derives support, at least, from the specification, Example 10; (page no. 27).

In light of the forgoing amendments and arguments, Applicants respectfully request the withdrawal of this rejection.

The Examiner has rejected Claims 1-2, 4-5, 7, 13-14, 16-17, 20-23 and 27-28 under 35 U.S.C. § 112, first paragraph, as purportedly lacking a written description. The Examiner alleges that the specification "fails to describe the structural features of these modified nucleic acids." Specifically, the Examiner has stated that the claims are broadly drawn to a multitude of DNA molecules, however, the specification only describes a coding sequence from *Camellia sinensis* that comprises SEQ ID NO:2, which encodes a full-length enzyme. Based thereon, the Examiner has stated that Applicant has not described DNA molecules that encode an N-methyl transferase within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention. The Examiner further alleges that "one skilled in the art would not have been in possession of the *genus* claimed at the time this application was filed." (Emphasis added)

> "[I]f an applicant disclosed an amino acid sequence, it would be unnecessary to provide an explicit disclosure of nucleic acid sequences that encoded that amino acid sequence. Since the genetic code is widely known, a disclosure of an amino acid sequence would provide sufficient information such that one would accept that an applicant was in possession of the full *genus* of nucleic acids encoding a given amino acid sequence..." (Emphasis added)

In re Bell, 991 F.2d 781, 785, 26 USPQ2d 1529, 1532 (Fed. Cir. 1993)

Applicants direct the Examiner's attention to the specification at pages 7-11 regarding the structural features and stringent hybridization conditions relating to these modified nucleic acids. Applicants submit that it is well within the purview of the skilled artisan to modify nucleotide sequences by deletion, substitution or insertion and then determine if such modified sequences maintain the desired enzymatic activity. Further, it is well within the purview of the skilled artisan to produce modified nucleotide sequences and determine if such modified sequences hybridize to the sequence of SEQ ID NO:1 under stringent conditions. Furthermore, it is well within the purview of the skilled artisan to determine if proteins encoded by these modified nucleic acids maintain the recited enzymatic activities. The genetic code is widely known and these types of experimentation are merely routine and do not constitute undue experimentation. The specification need not teach what is known in the art (e.g., modifying nucleic acid sequences). In fact, the Federal Circuit has stated that a patent need not teach, and preferably omits, what is well known in the art. *See Hybritech, Inc. v. Monoclonal Antibodies, Ind.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986).

Therefore, Applicants respectfully request withdrawal of the rejection of claims 1-2, 4-5, 7, 11-14 and 16-23 under 35 U.S.C. § 112, first paragraph.

Claims Rejected Under U.S.C. § 112, Second Paragraph:

The Examiner has rejected Claims 1-7, 11-14, 16-23 and 27-28 under U.S.C. § 112, second paragraph, as purportedly indefinite.

Claims 1 and 4 are rejected "because it is not clear if the DNA or RNA comprises both or either parts (a) and (b)." In order to expedite prosecution in the subject application, and not to acquiesce to the Examiner's rejection, Applicants have amended Claims 1 and 4 by replacing the phrase "any of the following" by phrase "either of the following."

Claims 1(b) and 4(b) are also rejected for reciting "obtained by carrying out nucleotide replacement, deletion, or insertion." The Examiner alleges these claims are indefinite because they do not adequately limit the number of nucleotide which are replaced or inserted.

Applicants assert that in light of the amendments made to Claims 1 and 4, and without conceding to the Examiner's rejection, the phrase "obtained by carrying out nucleotide replacement, deletion, or insertion" has been deleted without prejudice to or disclaimer of the subject matter therein. This rejection is thus respectfully moot.

Claims 1(b) and 4(b) are rejected for reciting "said modified sequence." The Examiner alleges that there are no antecedent basis for this phrase. Applicants have amended Claims 1(b) and 4(b) to recite "said modified nucleotide sequence" instead of "said modified sequence."

Claims 1(b) and 4(b) are rejected for reciting "said enzyme activities." The Examiner purports that there are no antecedent basis for this phrase. In order to expedite prosecution in the subject application, and not to acquiesce to the Examiner's rejection,

Applicants have amended Claims 1(b) and 4(b) to recite "said N-methyl transferase enzyme activities" instead of "said enzyme activities."

Claims 1(b) and 4(b) are further rejected for reciting "maintains said enzyme activities." The Examiner is allegedly not clear on what maintenance of an enzyme activity means. In order to expedite prosecution in the subject application, and not to acquiesce to the Examiner's rejection, Applicants have amended Claims 1(b) and 4(b) to read "possesses all of said N-methyl transferase enzyme activities" instead of "maintains said enzyme activities."

Claims 2 and 5 have been rejected for reciting "hybridized at a ... to overnight." The Examiner alleges that the claims are not clear as to the level of stringency required. In order to expedite prosecution in the subject application, and not to acquiesce to the Examiner's rejection, Applicants have amended these claims to recite "hybridized under stringent conditions at."

Claims 2 and 5 have also been rejected for not reciting the salt concentration at which hybridization may occur. In order to expedite prosecution in the subject application, and not to acquiesce to the Examiner's rejection, Applicants have amended these claims to include the limitation "2 x ssc" for salt concentration.

Claims 2 and 5 are further rejected for reciting "said nucleotide sequence (a) and said nucleotide sequence (b)." The Examiner alleges that this particular wording makes it appear that parent claim have both sequence (a) and (b). In order to expedite prosecution in the subject application, and not to acquiesce to the Examiner's rejection, Applicants have

amended these claims to recite "said nucleotide sequence (a) or said nucleotide sequence (b)" instead of "said nucleotide sequence (a) and said nucleotide sequence (b)."

Furthermore, the Examiner alleges that there is no antecedent basis for these claims as presently recited. In order to expedite prosecution in the subject application, and not to acquiesce to the Examiner's rejection, Applicants have amended Claims 2 and 5 to recite "in claim 4 wherein" instead of "in claim 4, wherein."

Claim 7 is rejected for reciting "said N-methyl transferase encoded by the DNA molecule." The Examiner alleges that there is no antecedent basis for Claim 7 as presently recited. In order to expedite prosecution in the subject application, and not to acquiesce to the Examiner's rejection, Applicants have amended Claim 7 to recite "N-methyl transferase encoded by the DNA molecule" instead of "said N-methyl transferase encoded by the DNA molecule."

Claim 23 is rejected for reciting "a transformed whole plant" allegedly without antecedent basis. The Examiner purports that the parent claim 20 makes no reference to a transformed whole plant. In order to expedite prosecution in the subject application, and not to acquiesce to the Examiner's rejection, Applicants have amended both Claim 20 and 23. Claim 20 has been amended to include the phrase "or whole plant." Claim 23 has been amended to read "said transformed whole plant" instead of "a transformed whole plant."

Withdrawal of this rejection is thus respectfully requested.

From the foregoing, further and favorable reconsideration in the form of a Notice of Allowance is believed to be next in order and such action is earnestly solicited.

In the event that there are any questions concerning this amendment, or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,

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Attachment to Reply and Amendment dated October 3, 2002

Marked-up Claims 1, 2, 4, 5, 7, 14, 17, 20, 21, 23, 27

1. (Twice Amended) An isolated DNA molecule comprising either ~~any~~ of the following nucleotide sequences:

(a) a nucleotide sequence encoding N-methyl transferase of SEQ ID NO:1 and having the N-methyl transferase ~~N-methyltransferase~~ enzyme activities of 7-methylxanthine N3 methyl transferase, theobromine N1 methyl transferase and paraxanthine N3 methyl transferase; or

(b) a modified nucleotide sequence ~~obtained by carrying out nucleotide replacement, deletion, or insertion in~~ which hybridizes under stringent conditions to the complementary sequence of said nucleotide sequence (a) where the ~~a~~ polypeptide encoded by said modified nucleic sequence ~~maintains~~ possesses all of said N-methyl transferase enzyme activities.

2. (Twice Amended) The isolated DNA molecule as claimed in claim 1~~,~~ wherein said nucleotide sequence (a) ~~and~~ or said modified nucleotide sequence (b) can be hybridized under stringent conditions at a temperature ranging from 40° to 80°C, at salt concentrations of 2 x ssc and for a time period ranging from several hours to overnight.

4. (Twice Amended) An isolated RNA molecule comprising either ~~any~~ of the following nucleotide sequences:

Attachment to Reply and Amendment dated October 3, 2002

Marked-up Claims 1, 2, 4, 5, 7, 14, 17, 20, 21, 23, 27

(a) a nucleotide sequence encoding N-methyl transferase of SEQ ID NO:1 and having the N-methyl transferase ~~N-methyltransferase~~ enzyme activities of 7-methylxanthine N3 methyl transferase, theobromine N1 methyl transferase and paraxanthine N3 methyl transferase; or

(b) a modified nucleotide sequence ~~obtained by carrying out nucleotide replacement, deletion, or insertion in~~ which hybridizes under stringent conditions to the complementary sequence of said nucleotide sequence (a) where the ~~a~~ polypeptide encoded by said modified nucleic sequence ~~maintains~~ possesses all of said N-methyl transferase enzyme activities.

5. (Twice Amended) The isolated RNA molecule as claimed in claim 4~~,~~ wherein said nucleotide sequence (a) ~~and~~ or said modified nucleotide sequence (b) can be hybridized under stringent conditions at a temperature ranging from 40° to 80°C, at salt concentrations of 2 x ssc and for a time period ranging from several hours to overnight.

7. (Thrice Amended) An expression vector comprising the DNA molecule as claimed in claim 1 and a promoter for expressing ~~said~~ N-methyl transferase encoded by the DNA molecule in plant cells.

14. (Twice Amended) The vector as claimed in claim 13, wherein the vector ~~encodes~~ expresses an N-methyl transferase with 7-methyl xanthine N3 methyl transferase,

Attachment to Reply and Amendment dated October 3, 2002

Marked-up Claims 1, 2, 4, 5, 7, 14, 17, 20, 21, 23, 27

theobromine N1 methyl transferase, and paraxanthine N3 methyl transferase activities in cells of at least one of microorganisms or plants.

17. (Thrice Amended) The ~~A~~ plant cell, plant tissue, or whole plant as claimed in claim 16, wherein the vector is introduced by infection.

20. (Twice Amended) A method for producing a plant secondary metabolite selected from the group consisting of 7-methyl xanthine, paraxanthine, theobromine and caffeine comprising: culturing the transformed plant cell, ~~or~~ plant tissue or whole plant as claimed in claim 16 to form a plant body, and culturing said plant body to produce a plant secondary metabolite, wherein said plant cell, ~~or~~ plant tissue or whole plant is ~~a Camellia or~~ a Coffea ~~coffea~~ plant cell, ~~or~~ plant tissue or whole plant.

21. (Thrice Amended) A method for modifying ~~a composition~~ the concentration of ~~a plant secondary metabolite~~ caffeine comprising: culturing the plant cell or plant tissue as claimed in claim 16 to form a plant body, and culturing said plant body to modify a composition of ~~a plant secondary metabolite~~ caffeine, wherein said plant cell or plant tissue is ~~a Camellia or~~ a ~~coffea~~ Coffea plant cell or plant tissue.

23. (Thrice Amended) The ~~A~~ method as claimed in claim 20, wherein said ~~a~~ transformed whole plant is ~~a Camellia or~~ a Coffea plant.

27. (Amended) A vector encoding the ~~an~~ RNA molecule as claimed in claim 4.